

Remarks

Claim 77 has been amended to correct a typographical error. No new matter is entered by way of this amendment.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 66-69 and 72-80 were rejected for allegedly lacking enablement. Although Applicants respectfully note that the present office action is unclear as to what the Examiner deems enabled or not enabled, Applicants note that in the Office Action mailed June 22, 2006, the Examiner stated that the claims are enabled for nerve growth factor. As held by *Invitrogen Corp. v. Clontech Labs* and *Johns Hopkins Univ. v. CellPro, Inc.*, the enablement requirement is met if the description enables any mode of making and using the invention. *Invitrogen Corp. v. Clontech Labs.*, 429 F.3d 1052 (Fed. Cir. 2005); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998). Thus the standard of enablement has been met by the Applicants.

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Amgen v. Hoechst Marion Roussel* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 165, 42 USPQ2d at 1004. The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, USPQ2d 1609, 1614 (Fed. Cir. 2002). In addition, a patent need not teach, and preferably omits, what is well known in the art. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, USPQ 81, 94 (Fed. Cir. 1986). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. *In re Wands*, 858 F.2d 731, 735, 736-737 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of

the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *In re Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (Pat. Bd. App. 1982). There is no requirement for working examples. *In re Borkowski*, 422 F.2d 904 (C.C.P.A. 1970). Further, patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). As set forth in *Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998), "the enablement requirement is met if the description enables any mode of making and using the invention." Thus, an Applicant is not legally required to prove enablement for each and every species that falls within the scope of the claim.

Claim 66 defines a fusion polypeptide comprising a collagen-binding domain and an epithelial cell proliferation-modulating agent, wherein the epithelial cell proliferation-modulating agent is selected from the group consisting of insulin, nerve growth factor (NGF), NGF receptor, epidermal growth factor (EGF) receptor, neu, inhibin α , inhibin β , Müllerian inhibitory substance, tumor necrosis factor (TNF)-receptor (type 1), TNF-receptor (type 2), wnt-2, and hepatocyte growth factor (HGF) receptor (c-met).

As described in the specification at least at page 4, lines 4-6, a fusion polypeptide comprising an epithelial cell proliferation-modulating agent and a collagen-binding domain is provided. As described on page 9, line 14 to page 10, line 13, collagen binding domains are well known to those of skill in the art. In addition, the epithelial cell proliferation-modulating agents, insulin, nerve growth factor (NGF), NGF receptor, epidermal growth factor (EGF) receptor, neu,

inhibin α , inhibin β , Müllerian inhibitory substance, tumor necrosis factor (TNF)-receptor (type 1), TNF-receptor (type 2), wnt-2, and hepatocyte growth factor (HGF) receptor (c-met), defined by the claims are also known to those of skill in the art, including their nucleic acid and amino acid sequences. The specification at least at page 14, lines 3-12 describes how to obtain nucleic acid sequences for making the fusion polypeptides defined by the claims. The specification at least at page 14, line 13 to page 24, line 19 describes in detail methods known to those of skill in the art for making fusion polypeptides such as the fusion polypeptides defined by the claims. In addition, the specification describes how to use such fusion polypeptides. As described in the specification at least at page 2, lines 20-24, it has been shown that collagen binding domains can be used to target molecules to specific tissues. Therefore, the specification describes methods of making and using collagen binding domains to target cell proliferation-modulating agents to tissues. The fusion polypeptides defined by the claims can be used to modulate epithelial cell proliferation as described in the specification at least at page 4, line 16 to page 5, line 2 and page 24, line 20 to page 25, line 11. As described in the specification at least at page 25, lines 12-21, modulation of epithelial cell proliferation includes regulating or controlling epithelial cell growth. As also described in the specification at least at page 25, cases in which it is desirable to modulate cell proliferation include hypertrophy or overgrowth of a cell population within a tissue or hypotrophy or lack of cells within a tissue. The specification describes uses for epithelial cell proliferation-modulating agents that inhibit cell proliferation or differentiation such as, for example, for inhibiting hypertrophic growth of a cell population (e.g., preventing cellular proliferation of a tumor; see, for example, page 31, lines 14-15). In addition, the specification describes uses for epithelial cell proliferation-modulating agents that induce cell growth or differentiation such as, for example, for promoting wound healing. The specification provides uses for epithelial cell proliferation-modulating agents that inhibit or promote epithelial cell proliferation and/or differentiation. As discussed above, there is no requirement for examples. However, as noted by the Examiner, the specification provides an example of how to make and use a fusion polypeptide comprising a collagen binding domain and an epithelial cell-proliferation stimulating agent. MPEP § 2164.04 provides that “[i]n order to make a rejection,

the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)...As stated by the court, 'it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.' 439 F.2d at 224, 169 USPQ at 370." The Examiner has provided no evidence as to why one of skill in the art would be unable to make and use the fusion polypeptides defined by the claims based on the guidance provided in the specification and working example. The specification includes uses of epithelial cell proliferation stimulating agents beyond just wound healing. Therefore, the agents defined by the claims are epithelial cell proliferation modulating agents and thus can be used to inhibit or stimulate cell proliferation and/or differentiation as desired as described in the specification.

Claims 67 defines the fusion polypeptide of claim 66, wherein the epithelial cell proliferation-modulating agent stimulates epithelial cell proliferation. EGF receptor, TNF receptor type I and type II and wnt-2 stimulate epithelial cell proliferation. The Examiner has provided no evidence to the contrary, which, as noted above, is required. As demonstrated by Kurada and White, *Apoptosis* 4(4):239-43 (1999) ("Kurada") (previously submitted) epidermal growth factor receptor promotes cell proliferation. As described in Kollias et al., *Ann. Rheum. Dis.* 58(Suppl. 1):I32-I39 (1999) ("Kollias"), (previously submitted), tumor necrosis factor (TNF) receptors mediate cellular proliferation and differentiation. Dale et al., *Cancer Res.* 56(19):4320-3 (1996) ("Dale") (previously submitted) states that wnt-2 induces mitosis of epithelial cells.

Claim 68 defines the fusion polypeptide of Claim 66, wherein the collagen-binding domain is a collagen-binding domain of von Willebrand factor. Claim 69 defines the fusion polypeptide of claim 68, wherein the collagen-binding domain of von Willebrand factor comprises the decapeptide WREPSFMALS (SEQ ID NO:1). The collagen binding domain of von Willebrand factor is known in the art and is described in the specification at least at page 9,

line 19 to page 10, line 13. The specification describes how to make and use fusion polypeptides comprising the collagen binding domain of von Willebrand's factor at least at page 14, line 13 to page 24, line 19 and the Examples.

Claim 72 defines a nucleic acid sequence encoding a fusion polypeptide comprising a collagen-binding domain and an epithelial cell proliferation-modulating agent, wherein the epithelial cell proliferation-modulating agent is selected from the group consisting of insulin, nerve growth factor (NGF), NGF receptor, epidermal growth factor (EGF) receptor, neu, inhibin α , inhibin β , Müllerian inhibitory substance, tumor necrosis factor (TNF)-receptor (type 1), TNF-receptor (type 2), wnt-2, and hepatocyte growth factor (HGF) receptor (c-met). As described above, nucleic acids encoding collagen binding domains are known in the art and described in the specification at least at page 9, line 14 to page 10, line 13. Nucleic acids encoding insulin, nerve growth factor (NGF), NGF receptor, epidermal growth factor (EGF) receptor, neu, inhibin α , inhibin β , Müllerian inhibitory substance, tumor necrosis factor (TNF)-receptor (type 1), TNF-receptor (type 2), wnt-2, and hepatocyte growth factor (HGF) receptor (c-met), defined by the claims are also known to those of skill in the art and can be obtained from GenBank, the National Institutes of Health computer database as described on page 14 of the specification. Other methods for obtaining the nucleic acids for use in making the fusion polypeptides are described in the specification at least at page 14, lines 3-12.

Claim 73 defines the nucleic acid sequence of claim 72 operably linked to a promoter. Methods for operably linking nucleic acids to a promoter are known to those of skill in the art and are described in the specification at least at page 16, lines 1-22.

Claim 74 defines an expression vector comprising the nucleic acid sequence of claim 72. Methods of making and using expression vectors comprising nucleic acids encoding fusion polypeptides are known in the art and are described in the specification at least at page 15, lines 1-23 and page 17, line 1 to page 18, line 23.

Claim 75 defines the expression vector of claim 74, wherein the expression vector is a retroviral vector. Methods for making and using retroviral vectors for gene expression are

known in the art and are described in the specification at least at page 15, lines 1-23 and page 23, lines 4-15.

Claim 76 defines a host cell comprising the nucleic acid sequence of claim 72. Methods for making and using host cells comprising nucleic acid sequences are known in the art and are described in the specification at least at page 15, lines 1-23, page 17, line 7 to page 18, line 2 and page 19, line 1 to page 22, line 14.

Claim 77 defines a method of producing the fusion polypeptide comprising a collagen-binding domain and an epithelial cell proliferation-modulating agent, comprising growing the host cells of claim 76 under conditions that allow expression of the fusion polypeptide and recovering the fusion polypeptide. Claims 78 and 79 define that the host is a prokaryotic cell or eukaryotic cell, respectively. Methods for producing fusion polypeptides, such as those defined by the claims using eukaryotic or prokaryotic host cells, are well known to those of skill in the art and are described in the specification at least at page 14, line 13 to page 22, line 20.

Claim 80 defines a pharmaceutical composition comprising a fusion polypeptide comprising a collagen-binding domain and an epithelial cell proliferation-modulating agent, in a pharmaceutically acceptable carrier, wherein the epithelial cell proliferation-modulating agent is selected from the group consisting of insulin, nerve growth factor (NGF), NGF receptor, epidermal growth factor (EGF) receptor, neu, inhibin α , inhibin β , Müllerian inhibitory substance, tumor necrosis factor (TNF)-receptor (type 1), TNF-receptor (type 2), wnt-2, and hepatocyte growth factor (HGF) receptor (c-met). Methods for making pharmaceutical compositions comprising the fusion polypeptides defined by the claims are described in the specification at least at page 30, line 17 to page 39, line 2. Methods for using pharmaceutical compositions are described in the specification at least at page 24, line 20 to page 31, line 27.

With respect to the Examiner's comments regarding claim 80 and *in vivo* use, to comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). In addition, as

set forth in MPEP § 2164.01(c), “the applicant need not demonstrate that the invention is completely safe.”

As set forth in *In re Brana*, “[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.” *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995). While the court in *In re Brana* referred to “usefulness” the rejection on appeal was for nonenablement. In *In re Cortright* 165 F.3d 1353 (Fed. Cir. 1999), the court held that “claims to a method of treating scalp baldness could be enabled even in the method did not produce a full head of hair.” The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988).

The Examiner's attention is also drawn to the fact that “[e]nabling does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions. Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the invention would lose the benefit of the patent bargain.” *Invitrogen Corp. v. Clontech Labs.*, 429 F.3d 1052 (Fed. Cir. 2005). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1614 (Fed. Cir. 2002).

The specification provides ample guidance for one of ordinary skill in the art to be able to make and use the fusion polypeptides defined by the claims. Therefore, claims 66-69 and 72-80 are enabled. Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicant : Frederick L. Hall et al.
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It is believed that no fee is due. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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Tina Williams McKeon
Reg. No. 43,791

Fish & Richardson P.C.
1180 Peachtree Street, N.E.
21st Floor
Atlanta, GA 30309
Telephone: (404) 892-5005
Facsimile: (404) 892-5002